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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/765,491	01/18/2001	Jack L. Arbiser	EU 98055 CON	8772

23579 7590 07/23/2007

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EXAMINER	
KIM, JENNIFER M	

ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
07/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/765,491	ARBISER, JACK L.	
	Examiner	Art Unit	
	Jennifer Kim	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-6,10-12 and 17-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-6, 10-12 and 17 -19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

In view of the amendment filed on May 29, 2007 PROSECUTION IS HEREBY REOPENED. The grounds for rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

Any rejection of record not addressed herein is withdrawn.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 4 is rejected under 35 U.S.C. 102(b) as being anticipated by Dezube et al. (1998).

Dezube et al. teach that angiogenesis is a major component of **Kaposi's sarcoma** (a skin disorder associated with lymphangiogensis) and a critical process in tumor growth. Dezube et al. teach that TNP-470 is a synthetic analog of **fumagillin**. (page 1444 right-hand column send paragraph). Dezube et al. teach that TNP-470, administered as a weekly, 1-hour infusion to patients with early Kaposi's sarcoma.

Claim 17 is rejected under 35 U.S.C. 102(b) as being anticipated by Eckhardt et al. (1996).

Eckhardt et al. teach **tecogalan sodium** is **a sulfated polysaccharide** isolated from the cell walls of the *bacterium Arthrobacter* sp. AT-25. (page 491, right-hand column first sentence of full paragraph). Eckhardt et al. teach that tecogalan sodium is an **angiogenesis inhibitor**. (summary, first sentence). Eckhardt et al. teach that the antiangiogenic effect of tecogalan sodium is thought to be medicated by the inhibition of binding of basic fibroblast growth factor to cellular receptors. Eckhardt et al. teach that the patient with refractory malignancies including **Kaposi's sarcoma** (a skin disorder

associated with lymphangiogenesis) is treated with tecogalan sodium infusion. (under summary). Eckhardt et al. teach that recommended angiogenesis inhibition dose of tecogalan sodium. (page 491, under conclusion).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dezube et al. as applied to claim 4 above, and further in view of Yanai et al. (U.S.Patent No. 5,422,363).

The teachings of Dezube et al. as applied as before.

Dezube et al. do not teach a topical administration of TNP-470.

Yanai et al. teach that pharmaceutical compositions with improved stability comprising a fumagillol derivative including TNP-470 is useful for treating diseases associated with angiogenesis including Kaposi's sarcoma (a skin disorder associated with lymphangiogenesis). (abstract. Bolumn 9, lines 50-65, column 10 Example 1). Yanai et al. exemplify a composition comprising TNP-470 (also known as 6-O-(N-Chloroacetylcarbamoyl)fumagillol) in a pharmaceutical composition. (column 10,

Example 1). Yanai et al. teach that these agents can be administered other than injections such as **external preparations**. (column 9, lines 22-28).

It would have been obvious to one of ordinary skill in the art to administer TNP-470 topically or externally for the treatment of Kaposi sarcoma (a skin disorder associated with lymphangiogenesis) because Dezube et al. teach that infusion of TNP-470 is useful for the treatment of Kaposi sarcoma and because Yanai et al. teach that TNP-470 can be administered other than injectable formulation for the treatment of Kaposi sarcoma. One would have been motivated to employ a topical route of TNP-470 for the treatment of Kaposi sarcoma in order to achieve an expected benefit of topical formulation that is formulated to improve the stability of TNP470 as taught by Yanai et al. There is a reasonable expectation of successfully treating Kaposi sarcoma with topical administration of TNP-470 because TNP-470 is effective for the treatment of Kaposi sarcoma and because TNP-470 can be administered topically for the same treatment with improved stability as taught by Yanai et al.

Claims 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yanai et al. (U.S.Patent No. 5,422,363).

Yanai et al. teach that pharmaceutical compositions with improved stability comprising **fumagillol derivatives** including TNP-470 are useful for **treating diseases associated with angiogenesis** including Kaposi's sarcoma (a skin disorder associated with lymphangiogenesis). (abstract. column 9, lines 50-65, column 10 Example 1). Yanai et al. exemplify a composition comprising TNP-470 (also known as 6-O-(N-

Chloroacetylcarbamoyl)fumagillol) in a pharmaceutical composition. (column 10, Example 1). Yanai et al. teach that these agents can be administered other than injections such as **external preparations**. (column 9, lines 22-28). Yanai et al. teach that fumagillol derivatives has low toxicity and exhibits potent pharmacological properties against diseases associated with angiogenesis. (column 9, lines 50-65).

Yanai et al. do not expressly illustrate the administration of fumagillol derivatives to inhibit symptoms associated with angiogenesis in the treatment of the **specific skin disorders** set forth in claims 4.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ **fumagillol derivatives** (fumagillin derivatives) for inhibiting symptoms associated with angiogenesis regardless of the type of skin disorders that causes angiogenesis symptoms set forth in claim 4 because Yanai et al. teach that fumagillol derivatives are exhibits potent properties against angiogenesis. It would have been obvious to one of ordinary skill in the art that any symptoms of angiogenesis would be expected to be treated with fumagillol derivatives having potent antiangiogenesis property regardless of the types of the disorder. There is a reasonable expectation of successfully treating "**symptoms associated with angiogenesis**" with fumagillol derivatives possessing **potent antiangiogenesis property** in view of Yanai et al.

Claims 4, and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Galardy et al. (U.S.Patent No. 5,268,384).

Galardy et al. teach that synthetic mammalian matrix metalloprotease inhibitors are useful in controlling angiogenesis. (abstract). Galardy et al. teach that the matrix metalloproteases inhibitors **inhibit** human skin **fibroblast collagenase**. These matrix metalloproteases inhibitors read on with Applicant's angiogenesis inhibitors such as **"collagenase inhibitors"** set forth in claim 4 because these matrix metalloproteases inhibitors have **both angiogenesis and collagenase inhibiting properties**. (column 2, lines 24-28). Galardy et al. teach that conditions that benefit from **angiogenesis inhibition** include cancer, angiosarcoma, **Kaposi's sarcoma** and **skin conditions**, such as cavernous hemangioma and psoriasis. (column 13, lines 40-50). Galardy et al. teach that for localized conditions, "collagenase inhibitors" are preferred to administered **topically**. (column 13, lines 28-30). Galardy et al. teach that **effective amounts** of "collagenase inhibitors" to be formulated. (column 12, lines 53-65).

Galardy et al. do not expressly illustrate the administration of matrix metalloprotease inhibitors (collagenase inhibitors) to inhibit symptoms associated with angiogenesis in the treatment of the **specific skin disorders** set forth in claims 4.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ matrix metalloprotease inhibitors (collagenase inhibitors) for inhibiting symptoms associated with angiogenesis in the treatment of skin disorders associated with lymphangiogenesis (Kaposi's sarcoma) because Galardy et al. teach that matrix metalloprotease inhibitors are collagenase inhibitors useful for controlling angiogenesis and because Kaposi's sarcoma is one of conditions that benefit from angiogenesis inhibition. Applicant is reminded that Kaposi's sarcoma disclosed by

Galardy et al. is a skin disorders associated with lymphangiogensis as admitted by Applicant. One would have been motivated to employ matrix metalloprotease inhibitors (collagenase inhibitors) for the treatment of Kaposi's sarcoma (a skin disorder associated with lymphangiogenesis) in order to achieve a beneficial antiangiogenic effect of collagenase inhibitors taught by Galardy et al. There is a reasonable expectation of successfully treating skin disorders associated with lymphangiogenesis such as Kaposi's sarcoma with collagenase inhibitors taught by Galardy et al. because these compounds are known to have antiangiogenesis effect that is taught to be beneficial in treating Kaposi's sarcoma.

With respect to inhibiting **symptoms associated with angiogenesis** in the treatment of other skin disorders such as Sturge-Weber syndrome, verruca vulgaris, tuberous sclerosis, venous ulcers, molluscum contagious, seborrheic keratosis, and actinic keratosis set forth in claim 4 is obvious because Galardy et al. teach that collagenase inhibitors are **useful in controlling angiogenesis and useful in conditions that benefit from angiogenesis inhibition involving skin conditions**. It would have been obvious to one of ordinary skill in the art to employ collagenase inhibitors for inhibiting symptoms associated with angiogenesis in a treatment of any skin disorders regardless of its origin (types the skin disorders) because Galardy et al. teach that collagenase inhibitors have antiangiogenesis property. Therefore, it is expected that these compounds would treat at least symptoms of angiogenesis at any disorder. Therefore, one would have been motivated to employ collagenase inhibitors for the treatment of any angiogenesis associated symptoms regardless of the origin of

the disorder that causes the angiogenesis symptoms. There is a reasonable expectation of successfully inhibiting symptoms associated with angiogenesis in the treatment of a skin disorders administering collagenase inhibitors because collagenase inhibitors have the specific activity that is beneficial for treating symptoms of antiangiogenesis.

Claims 10-12 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aggarwal (WO 95/18606) of record in view of Dorland's Illustrated Medical Dictionary, 28th Edition (1994).

Aggarwal teaches method for the treatment of melanomas comprising administration of effective dose of curcumin (mixture of demethoxycurcumin). (page 5, lies 20-32, page 6). Aggarwal teaches the composition comprising curcumin can be formulated topical in ointment form. (page, 7, lines 26-28, page 8, lines 7-15). Aggarwal teaches the effective dose of curcumin and curcumin analogues are administered in a dose of from about 1 microgram to about 100milligram. (page 6, lines 6-11).

Aggarwal do not expressly illustrate treatment of malignant melanoma the specific formulation set forth in claim 10.

Dorland's Illustrated Medical Dictionary, 28th Edition (1994), (Dorland's), teaches the term melanoma refers to malignant melanoma. (page 1004, under melanoma).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ curcumin composition comprising mixture of

demethoxycurcumin taught by Aggarwal in the treatment of malignant melanoma because Aggarwal teaches that the composition comprising curcumin in a mixture of demethoxycurcumin is useful for treating melanomas and because the term melanomas is referred to as malignant melanoma in view of Dorland's. There is a reasonable expectation of successfully treating malignant melanoma by administering Aggarwal's curcumin comprising demethoxycurcumin mixture because Aggarwal teaches that the composition is useful for treating melanoma also known as malignant melanoma in view of Dorland's. Further, It would have been obvious to one of ordinary skill in the art to modify the composition taught by Aggarwal in topical ointment formulation with effective range of curcumin for the treatment of malignant melanoma because Aggarwal teach curcumin composition can be formulated in topical ointment formulation with effective amount about 1 microgram to about 100milligrams and because Aggarwal teach curcumin is useful for the treatment of melanoma also known as malignant melanoma in view of Dorland's. One would have been motivated to make such a modification in order to successfully treating malignant melanoma with topical curcumin formulation taught by Aggarwal.

Claims 10-12 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arbiser et al. (June 1999) of record in view of Singh et al. (1996) and further in view of Aggarwal (WO 95/18606) of record.

Arbiser et al. on the abstract, teach that patients with recessive dystrophic epidermolysis bullosa (RDEB) are suggested to treat with angiogenesis inhibitors.

Arbiser et al. teach that the patients with RDEB have elevated levels of **basic fibroblast growth factor (bFGF)** and that **angiogenesis inhibitors may antagonize the effects of bFGF**. Arbiser et al. teach that there are currently no other means of treatment of disorder, which has a high morbidity and mortality rate. Arbiser et al. teaches that the patient with **RDEB** have a great increased risk of cutaneous **squamous cell carcinoma**. Arbiser et al. teach that patients with RDEB contribute development of **squamous cell carcinoma**.

Arbiser et al. lack curcumin and demethoxycurcumin and specific formulation set forth in claim 10.

Singh et al. teach that curcumin inhibits the growth of HUVEC stimulated with **fibroblast growth factor** that leads to **angiogenesis.** (abstract).

Aggarwal teach a composition comprising curcumin can be formulated topically in an ointment form. (page 7, lines 26-28, page 8, lines 7-15). Aggarwal teach the effective dose of curcumin and curcumin analogues are administered in a dose of form about 1 microgram to about 100 milligram. (page 6, lines 6-11). Aggarwal teach a method for the treatment of **squamous cell carcinoma** comprising administration of effective dose of curcumin (mixture of demethoxycurcumin). (page 5, lines 20-32, page 6).

It would have been obvious to one of ordinary skill in the art to employ curcumin or curcuminoids (i.e. demethoxycurcumin) for the treatment of the symptoms associated with elevated basic fibroblast growth factor in RDEB with topical formulation of curcumin taught by Aggarwal because Arbiser et al. suggested that angiogenesis inhibitors are

effective in the treatment of RDEB by antagonizing elevated levels of bFGF in RDEB patients and because curcumin or curcuminoids possess angiogenesis inhibiting property including inhibition of fibroblast growth factor as taught by Singh et al. It is noted that Arbiser et al. teach that the condition of RDEB with elevated bFGF contribute to the development of squamous cell carcinoma in a patient. One of ordinary skill in the art would have been motivated to employ Aggarwal's composition comprising curcuminoids for the treatment of RDEB because Aggarwal's composition is an effective antiangiogenesis inhibitor and it also has beneficial effect of treating squamous carcinoma that can be further develop from RDEB. There is a reasonable expectation of successfully treating symptoms associated with elevated bFGF in RDEB with curcumin composition taught by Aggarwal because there is a suggestion from Arbiser that any angiogenesis inhibitor can be employed to antagonize the level of bFGF and because curcumin is not only an antiangiogenesis inhibitor but it also conveniently treats squamous carcinoma that can be develop from RDEB condition as taught by Arbiser et al. Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Kim whose telephone number is 571-272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sreenivasan Padmanabhan
Supervisory Primary Examiner
Art Unit 1617

Jmk
July 19, 2007